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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,485	10/17/2001	Brenda F. Baker	RTS-0139	5056

7590 01/12/2005

Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
EPPS FORD, JANET L	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,485	BAKER ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. Applicant's arguments with respect to claims 1-2, and 4-10 and 12-14 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al. (WO 94/29486-A1).

5. The instant claims are drawn to a compound 8 to 80 nucleobases in length targeted to nucleobases 381 through 882 of a coding region of a nucleic acid molecule encoding matrix metalloproteinase 1 (SEQ ID NO: 3), wherein said compound specifically hybridizes with said region and inhibits the expression of matrix metalloproteinase 1.

6. Evans et al. disclose an oligonucleotide of 18 nucleotides in length comprising a sequence that is 100% complementary (i.e. antisense) to nucleotides 863 through 876 of the nucleic acid of SEQ ID NO: 3 of the instant application. (See Evans et al. page 66, Example 4,

STS primer cSRL-2d7-tA). However, the Evans et al. reference does not teach wherein the disclosed oligonucleotide functions to inhibit the expression of matrix metalloproteinase 1.

The oligonucleotide of Evans et al. exhibits 100% local similarity between nucleobases 381 through 882 of a coding region of a nucleic acid molecule encoding matrix metalloproteinase 1 SEQ ID NO: 3 of the instant invention. Given this high degree of similarity, the oligonucleotide targeted to matrix metalloproteinase 1 disclosed by Evans et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding matrix metalloproteinase 1 as defined in the instant specification at page 8, line 31 through page 9, line 13. Accordingly, the oligonucleotide disclosed by Evans et al. would specifically hybridize to bases 381 through 882 of SEQ ID NO: 3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an

Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide disclosed by Evans et al. would or would not have the additional functional limitation of "inhibiting expression" of matrix metalloproteinase 1 under general any assay conditions.

Therefore, absent evidence to the contrary, Evans et al. anticipate claims 1-2.

7. Claims 1-2, 4-6, 8, 10, and 12-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Wraight et al. (WO-200078341-A1).

Wraight et al. disclose an antisense oligonucleotide: 5'-AAGCCTGAGCAAGAT –3', that is 15 nucleobases in length (see page 82, line 42), and 93.3% complementary to nucleobases 607 through 621 of SEQ ID NO: 3 of the instant application.

The nucleic acid molecules of the Wraight et al. that are in the form of an antisense molecule may be linear or covalently closed circular and single stranded or partially double stranded. A double stranded molecule may form a triplex with target mRNA or a target gene. The molecule may also be protected from, for example, nucleases, by any number of means such as using a nonionic backbone or a phosphorothioate linkage. A convenient nonionic backbone contemplated herein is ethylphosphotriester linkage or a 2'-O-methylribosyl derivative. Alternatively or in addition to, the pyrimidine bases are modified by the inclusion of a C-5 propyne substitution which modification is proposed to enhance duplex stability. (see page 24, lines 9-20). In accordance with one aspect of the Wraight et al. invention, the antisense compounds are topically applied in an aqueous solution or in conjunction with a cream,

ointment, oil or other suitable carrier and/or diluent (see page 26, lines 11-13). The nucleic acid molecules may be administered in dispersions prepared in creams, ointments, oil or other suitable carrier and/or diluent such as glycerol, liquid polyethylene glycols and/or mixtures thereof (see page 28, lines 12-14). Moreover, the carriers of the invention can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils (see page 28, lines 20-23). However, the Wraight et al. reference does not teach wherein the disclosed oligonucleotide functions to inhibit the expression of matrix metalloproteinase 1.

The oligonucleotide of Wraight et al. exhibits 93.3% local similarity between nucleobases 381 through 882 of a coding region of a nucleic acid molecule encoding matrix metalloproteinase 1 SEQ ID NO: 3 of the instant invention. Given this high degree of similarity, the oligonucleotide targeted to matrix metalloproteinase 1 disclosed by Wraight et al. meets the structural limitations of the claimed invention and would be expected to "specifically hybridize" with a nucleic acid molecule encoding matrix metalloproteinase 1 as defined in the instant specification at page 8, line 31 through page 9, line 13. Accordingly, the oligonucleotide disclosed by Wraight et al. would specifically hybridize to bases 381 through 882 of SEQ ID NO: 3 as claimed.

The burden of establishing whether the prior art oligonucleotide has the further function of inhibiting gene expression under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a

prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the oligonucleotide disclosed by Wraight et al. would or would not have the additional functional limitation of "inhibiting expression" of matrix metalloproteinase 1 under general assay conditions.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-2, 4-10, and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wraight et al. in view of Monia et al.

The discussion of Wraight et al. as set forth above is incorporated here. However, Wraight et al. does not disclose antisense oligonucleotides comprising a 2'-O-methoxyethyl

sugar modification, a 5-methyl cytosine nucleobases modification, or wherein the antisense oligonucleotide is a chimeric oligonucleotide. Additionally, Wraight et al. does not specifically teach pharmaceutical compositions further comprising a colloidal dispersion system.

Monia et al. teach the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6). Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Wraight et al. and Monia et al. to design the compounds and compositions according to the present invention. One of ordinary skill in the art would have been motivated to modify the antisense compounds of Wraight et al. to comprise 2'-O-methoxyethyl sugar modifications, 5-methylcytosine modified nucleobases, or wherein said antisense compound is a chimeric compound, because according to Monia et al. antisense oligonucleotides comprising these modifications would enhance the cellular properties of antisense

oligonucleotides as compared to unmodified antisense compounds. Moreover, one of ordinary skill in the art would have been motivated to design compositions comprising the antisense compounds according to the present invention and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system because Monia et al. teach that compositions designed according to this manner would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Therefore, the invention as a whole is *prima facie* obvious over Wraight et al. in view of Monia et al.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600